Two–year survival, mental, and motor outcomes after cardiac extracorporeal life support at less than five years of age

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Supplemental material is available online.

Objective: Comprehensive outcome assessment of children receiving cardiac extracorporeal life support.

Methods: From 2000 to 2004, 39 consecutive children (aged 1 day to 4.4 years) had cardiac extracorporeal life support. Neurodevelopmental follow-up of all survivors was performed more than 6 months after life support (aged 53 ± 12 months). Developmental delay was defined as a score of less than 70 on the Bayley Scales of Infant Development II or Wechsler Preschool and Primary Scale of Intelligence. Predictor variables for mortality (at 2 years' follow-up) and delay were examined by univariate and multivariate analyses.

Results: Indications for extracorporeal life support were progressive low cardiac output in 14 (36%), failed weaning from cardiopulmonary bypass in 13 (33%), cardiac arrest in 9 (23%), and hypoxia in 3 (8%). Cardiac anatomy was single ventricle in 16 (41%), biventricular in 21 (54%), and myocarditis in 2 (5%). Survival was 18 (46%) at hospital discharge and 16 (41%) at 2 years. In survivors, mental score was 73 ± 16 (normal 100 ± 15), and 8 (50%) had mental delay. Initiating extracorporeal life support during cardiopulmonary resuscitation and duration of this resuscitation were not associated with death or mental delay. On multivariable Cox regression, lactate on admission to the pediatric intensive care unit (hazard rate 1.13; 95% confidence intervals 1.08–1.27) and single ventricle anatomy (hazard rate 3.93; 95% confidence intervals 1.62–9.49) were associated with death at 2 years. Stepwise multiple regression found time for lactate to normalize on extracorporeal life support, highest inotrope score during 120 hours of life support, and chromosomal abnormality explained 76.7% of the variance in mental score.

Conclusion: Cardiac extracorporeal life support had a 41% 2-year survival. Potentially modifiable variables (time for lactate to normalize and highest inotrope score early during extracorporeal life support) explained 69% of mental score variance.

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Extracorporeal life support (ECLS) has become an accepted therapeutic modality for neonates and children with progressive respiratory and/or cardiac failure that is refractory to conventional management.[1] The first use of ECLS to provide cardiac assistance after surgery for congenital heart disease was reported in 1970, but since the early years of ECLS, the predominant application has been for neonatal respiratory failure.[2] Over the past decade, however, there has been a significant increase in the use of cardiac-related ECLS reported to the Extracorporeal Life Support Organization international registry. Currently, ECLS is used as a bridge to recovery in patients with severe low cardiac output syndrome after surgery for congenital heart disease and in nonsurgical conditions such as myocarditis and dysrhythmias. As well, ECLS is used as a bridge to cardiac transplantation in children with

Abbreviations and Acronyms

CI = confidence intervals
CPB = cardiopulmonary bypass
CPR = cardiopulmonary resuscitation
ECLS = extracorporeal life support
HR = hazard rate
MAHSC = The Multiattribute Health Status Classification System
OR = odds ratio
PICU = pediatric intensive care unit
SD = standard deviation

cardiomyopathy and patients who have not had significant recovery of cardiac function postoperatively.

More than 20,000 neonates worldwide have undergone ECLS for respiratory failure in the past 20 years, and many publications are available regarding the outcome of these neonates.[1] These data reveal an overall survival of approximately 75% with an incidence of long-term neurologic dysfunction in survivors of between 15% and 30%.[3-5] Less than half as many neonates and children worldwide have received ECLS for cardiac indications,[1] with some recent single-center reports of survival between 30% and 55% (overall 40%).[6-8] The long-term neurodevelopmental outcomes of these cardiac ECLS patients have not been widely studied, although some series have described an incidence of long-term neurologic deficits in 40% to 60% of survivors.[9-11]

Our objective was to evaluate the long-term neurodevelopmental outcome in young patients receiving cardiac-related ECLS over a 5-year period and to identify any predictors of adverse neurologic outcomes or death in these patients.

Patients and Methods

This study uses data from an interprovincial inception cohort outcomes study conducted in three provinces in Western Canada. All patients under 5 years of age who received ECLS from January 2000 through December 2004 were identified at the time of ECLS. In all cases, ECLS was performed at the Stollery Children's Hospital, Edmonton, Alberta, Canada.

Demographic and some overall hospitalization variables that were previously agreed on were collected prospectively.[12] Several pre-ECLS, ECLS, and post-ECLS variables (Table E1) were added to the database by retrospective chart review. Long-term follow-up was discussed with parents or guardians once survival was probable. With their consent, contact was made with their respective follow-up clinics at the tertiary site of origin.

Patients

All consecutive patients given venoarterial cardiac-related ECLS at an age of less than 5 years over the 5-year period were registered. There were no exclusion criteria. All survivors received multidisciplinary neurodevelopmental assessments through existing neonatal follow-up clinics in Edmonton and Calgary, Alberta; Regina and Saskatoon, Saskatchewan; and Winnipeg, Manitoba. Ethics board approvals were obtained from each site before onset of the study. All parents or guardians signed individual consent forms.

Early Childhood Assessments

Outcomes assessment was completed at least 6 months after ECLS. At assessment, a research nurse recorded history of hospitalizations, illnesses, medication use, and need for supplemental oxygen. Physical measurements were obtained as has been described.[12] The family socioeconomic status was determined by the Blishen Index, a formula considering the relative income, needed education, and prestige factor of employment with a population mean and standard deviation (SD) of 43 (13).[13] Maternal education was indicated by years of schooling. Pediatricians experienced in neurodevelopmental follow-up examined each child for evidence of cerebral palsy[14] or visual impairment, defined as corrected visual acuity in the better eye of less than 20/60.[12] Hearing was evaluated by experienced certified pediatric audiologists in soundproof environments, as has been described.[12] Hearing impairment was defined as binaural sensorineural hearing loss of more than 40 dB hearing level at any frequency from 250 to 4000 Hz for children under 2 years; for older children, bilateral responses greater than 25 dB hearing level within the same frequencies were considered impaired. Motor or sensory disability was defined as cerebral palsy, visual impairment, or sensorineural hearing impairment as defined herein. Certified pediatric psychologists and psychometrists administered The Bayley Scales of Infant Development II in those assessed at 42 months of age or less (n = 5).[15] This is a widely accepted standardized outcome measure used in neonatal follow-up clinics yielding a mental standardized score (developmental quotient) with a mean of 100 and an SD of 15. A developmental quotient of less than 70 (2 SD below the mean) indicates mental delay. Within a normative sample, 2.27% of children have scores of less than 70. The full scale intelligence quotient of the Wechsler Preschool and Primary Scale of Intelligence (third edition[16]) was used for those assessed after 48 months of age. This is a widely accepted standardized score with a mean of 100 and an SD of 15.[16] An intelligence quotient of less than 70 (2 SD below the mean) indicates mental delay. The parent completed Adaptive Behavior Assessment System, second edition, for children before the sixth birthday. General Adaptive Composite score with a mean of 100 and an SD of 15 was used to support the tested findings. The Multiattribute Health Status Classification System (MAHSC) parental questionnaire with each of 8 domains coded as normal or abnormal was recorded.

Statistics

Demographic variables included age at time of ECLS, weight on admission to the pediatric intensive care unit (PICU), gender, chromosomal abnormality, socioeconomic status, and mother's year of schooling. Pre-ECLS variables included the following: cardiac diagnoses, cardiopulmonary resuscitation (CPR), seizure, plasma lactate, inotrope score,[17] pediatric logistic organ dysfunction score,[18] cardiopulmonary bypass (CPB) time, aortic crossclamp time, and deep hypothermic circulatory arrest time for those having cardiac surgery before ECLS, whether ECLS was used after cardiac surgery or not, and indication for ECLS (failure to wean off CPB in the operating room, progressive low cardiac output syndrome, progressive low cardiac output syndrome with refractory hypoxia, or ongoing failed CPR). ECLS variables were recorded daily for up to 120 hours

of ECLS support. They included cannulation site, left-sided vent, use of a hemofilter for renal dialysis, plasma lactate (including the time for lactate to return to normal levels ≤ 2 mmol/L, inotrope score, pediatric logistic organ dysfunction score, blood flow on ECLS, fluid balance on ECLS, amount of packed red blood cells and platelet transfusions, plasma free hemoglobin, seizures, and the duration of ventilation and hospitalization. The primary outcomes of interest were the survival and mental score. The secondary outcomes included health and growth measures of morbidity, including height, weight, head circumference, use of supplemental oxygen, special diet or gastrostomy tube, long-term cardiac or pulmonary medication, and behavioral concerns.

The patients were divided into three groups for descriptive purposes: single ventricle anatomy, biventricular anatomy, and myocarditis. For comparison of groups, the χ^2 test and Fisher exact test (2-sided) were used. Bonferroni correction was applied. Forward multivariable Cox regression was used to examine which variables significant at a P value of ≤ .10 on univariate analysis were predictive of death by 2 years. For death by 10 days, given the short follow-up time, we used multiple logistic regression. Forward multiple logistic regression was also used to examine which variables significant at a P value of ≤ .10 on univariate analysis were predictive of mental delay. Sequential stepwise multiple regression was used to explore the overall greatest proportion of mental score outcome explained by a combination of predictors to a significance level of .05. SAS version 9.1 (SAS Institute, Inc, Cary, NC) was used for analyses.

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Results

Description of Cohort

Thirty-nine patients had cardiac-related ECLS. The patients having cardiac surgery before ECLS were 31 (3.0%) of the 1025 total patients under 5 years old having cardiac surgery with CPB in the study time period. There were 16 (41%) patients with single ventricle anatomy, including 13 with hypoplastic left heart syndrome. There were 21 (54%) with biventricular anatomy, including transposition of the great arteries (n = 4), total anomalous pulmonary venous connection (n = 6), and other lesions (n = 11). There were 2 (5%) with myocarditis. Complete follow-up data were available for all patients. With Bonferroni correction, demographic, pre-ECLS, and ECLS variables showed no statistically significant differences among the three groups (Table E1).

Description of the Outcomes

Survival outcomes are shown in Table 1. The survival to hospital discharge was 18 (46%) of 39, and the 2-year survival was 16 (41%) of 39. Twenty-two (56%) patients survived to be decannulated from ECLS. There were no statistically significant differences in mortality among the three groups of patients (Table 1).

We found no adverse outcome in 7 (18%), disability in 9 (23%), and death by 2 years in 23 (59%) of this cohort. General health outcomes in the 16 long-term survivors are shown in Table 2. Cerebral palsy occurred in 2 (12.5%) of the 16. Poor growth, long-term pulmonary medication, and long-term cardiac medication were not uncommon. Fourteen (88%) of the 16 survivors had behavioral concerns: behavioral abnormalities were noted by physicians in 10 (62.5%) of 16 survivors; parents reported behavioral concerns on the MAHSC in 11 (69%) of the 16. There were no statistically significant differences in these outcomes among the three groups of patients (Table 2).

Neurodevelopmental outcomes in the 16 long-term survivors are shown in Table 3. Follow-up was achieved in all survivors and performed at a mean age of 53 ± 12 months. The mental score was 73 ± 16 and ranged from less than 55 to 116, being significantly skewed to the left compared with the normal population (Figure 1). The adaptive-behavioral questionnaire completed by parents supports these tested results with a General Adaptive Composite score of 79 ± 19. There were no statistically significant differences in these outcomes among the three groups of patients (Table 3). Parents of many of the survivors had concerns on the MAHSC, particularly in the areas of cognition and behavior; the single ventricle survivors all had parental concerns in the areas of mobility, emotion, and self-care (Table 3). Overall, 8 (50%) survivors had mental delay (mental score < 70); all 3 survivors with chromosomal abnormality had delay, and 5 (38%) of the 13 without chromosomal abnormality had delay. In the 8 mentally delayed survivors, 1 had a score greater than 3 SD below the mean and had del22q11.2; the other 7 had scores between 2 SD and 3 SD below the mean, 2 of whom had a chromosomal abnormality (22 duplication, Turner mosaic).

Prediction of the Outcomes: Univariate Analyses

A univariate Cox regression indicates the following variables were associated with death by 2 years at a P value of ≤ .10: hospitalization days, lactate on admission to the PICU, platelets given over the first 120 hours of ECLS (milliliters per kilogram per day), packed red blood cells given over the first 120 hours of ECLS (milliliters per kilogram per day), single ventricle anatomy, ventilator days, pre-ECLS highest lactate, admission weight, and seizures (Table 4). A univariate logistic regression indicated that lactate on admission to the PICU (odds ratio [OR] 1.12; 95% confidence intervals [CI] 0.99–1.27; P = .084) and single ventricle anatomy (OR 8.17; 95% CI 1.41–47.22; P = .019) were associated with death at 10 days or less at a P value of ≤ .10. We also compared dichotomous variables between survivors with and without mental delay, and the only significant variable was chromosomal abnormality: 3 (43%) of 7 with delay versus 0 (0%) of 9 without delay (P = .063). Finally, the continuous variables were examined for their correlation with the mental score in the 16 survivors; correlations significant at the P < .10 level are shown in Table E2.

CPR before ECLS occurred in 3 (33%) of 9 who died by 10 days or less, 4 (29%) of 14 who died by 30 days or less, and 7 (30%) of 23 who died by 2 years. This compares

TABLE 1. Survival outcomes of the 39 patients after cardiac-related ECLS at less than 4.5 years of age, by type of heart lesion

	Total (n = 39)	Single ventricle (n = 16)	Biventricle (n = 21)	Myocarditis (n = 2)	χ^2	*P* value
Reason for coming off ECLS					6.584	.160
Withdrawal	17 (44%)	10 (63%)	6 (29%)	1 (50%)		
Decannulation	21 (54%)	5 (31%)	15 (71%)	1 (50%)		
Transplant	1 (3%)	1 (6%)	0 (0%)	0 (0%)		
Death by ≤ 10 days	9 (23%)	7 (44%)	2 (10%)	0 (0%)	6.625	.036
Death by hospital discharge	21 (54%)	12 (75%)	8 (38%)	1 (50%)	4.989	.083
Death by 2 y	23 (59%)	12 (75%)	10 (48%)	1 (50%)	2.884	.236

ELCS, Extracorporeal life support. *Withdrawal* refers to removal of ECLS with the expectation of death shortly thereafter; *decannulation* refers to removal of ECLS with expectation of survival being likely without ECLS; and *transplant* refers to removal of ECLS after successful heart transplantation.

with CPR before ECLS, occurring in 9 (30%) of 30, 8 (32%) of 25, and 5 (31%) of 16 who were survivors at these time points, respectively (P = not significant). Similarly, ECLS was initiated during ongoing CPR in 2 (22%) of 9 with death at 10 days or less, 3 (21%) of 14 with death at 30 days or less, and 6 (26%) of 23 with death by 2 years, compared with 7 (23%) of 30, 6 (24%) of 25, and 3 (19%) of 16 who were survivors at these time points, respectively (P = not significant). The duration of CPR in the 12 patients who had CPR before ECLS was not associated with death at 2 years: 30 ± 20 minutes in deaths versus 30 ± 25 minutes in survivors (P = .943). Moreover, CPR before ECLS with mental delay (2/7; 39%) versus without mental delay (3/9; 33%; P = .999), and CPR while initiating ECLS with mental delay (1/7; 14%) versus without mental delay (2/9; 22%; $P > .2$) were not associated with mental delay. Finally, the duration of CPR was not significantly different in those with mental delay or not (13.5 ± 25.7 vs 5.8 ± 11.2 minutes; P = .45), and the duration of CPR did not correlate with the mental score ($r = -0.208$; P = .74). Of the 5 survivors who had CPR before ECLS, 2 had a mental score of 55 to 69, 2 a score of 70 to 84, and 1 a score of 85 to 99.

Prediction of the Outcomes: Multivariate Analyses

To predict death by 2 years, we entered all variables significant at $P \leq .10$ on univariate analysis (Table 4) into a forward multivariable Cox regression. After adjustment for hospital duration and single ventricle anatomy, lactate on admission to the PICU was associated with death with a hazard rate (HR) of 1.17 (95% CI 1.08–1.27) (P = .0001) (Table 4). Patients with single ventricle anatomy died at about 3.9 times the rate of those without single ventricle anatomy

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TABLE 2. General health outcomes of 16 surviving children after cardiac ECLS at < 4.5 years of age, by type of heart lesion

	Total (n = 16)	Single ventricle (n = 4)	Biventricle (n = 11)	Myocarditis (n = 1)	χ^2	*P* value
Spastic left hemiparesis	2 (13%)	1 (25%)	1 (9%)	0 (0%)	1.206	.547
Vision loss	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
Sensorineural hearing loss						
Bilateral	1 (6%)	1 (25%)	0 (0%)	0 (0%)		
Unilateral	1 (6%)	0 (0%)	1 (9%)	0 (0%)		
Epilepsy	1 (6%)	0 (0%)	1 (9%)	0 (0%)		
Strabismus	2 (13%)	1 (25%)	1 (9%)	0 (0%)		
Behavioral diagnosis by						
Pediatrician	8 (50%)	1 (25%)	6 (55%)	1 (100%)	2.318	.677
Psychiatrist	2 (13%)	1 (25%)	1 (9%)	0 (0%)		
Respiratory examination abnormal	6 (38%)	1 (25%)	5 (45%)	0 (0%)	1.164	.559
Length < 3rd percentile	2 (13%)	1 (25%)	1 (9%)	0 (0%)		
Weight < 3rd percentile	3 (19%)	2 (50%)	1 (9%)	0 (0%)		
Head circumference < 2 SD (Nellhause)	3 (19%)	2 (50%)	1 (9%)	0 (0%)		
Vocal cord paralysis	2 (13%)	1 (25%)	1 (9%)	0 (0%)		
Gastrostomy > 2 y	3 (19%)	1 (25%)	2 (18%)	0 (0%)		
Supplemental continuous oxygen at > 4 y	1 (9%)	0 (0%)	1 (9%)	0 (0%)		
Long-term pulmonary medication	4 (25%)	1 (25%)	3 (27%)	0 (0%)	0.364	.834
Long-term cardiac medication	9 (56%)	3 (75%)	6 (55%)	0 (0%)	1.870	.393

ELCS, Extracorporeal life support; *SD,* standard deviation.

TABLE 3. Childhood neurodevelopmental outcomes after cardiac-related ECLS at less than 4.5 years of age, by heart lesion

	Total (n = 16)	Single ventricle (n = 4)	Biventricle (n = 11)	Myocarditis (n = 1)	F or χ^2	*P* value
DQ or IQ	73 (16)	73 (29)	73 (12)	72	0.001	.970
Mental delay < 70	8 (50%)	3 (75%)	5 (46%)	0 (0%)	2.091	.352
ABAS GAC	79 (19)	76 (29)	78 (17)	95	0.719	.412
Motor and/or sensory disability (with mental delay)	2 (12.5%)	1 (25%)	1 (9%)	0 (0%)		
MAHSC, % abnormal						
Sensation	5 (31%)	2 (50%)	3 (27%)	0%	1.19	.552
Mobility	8 (50%)	4 (100%)	4 (36%)	0%	5.818	.055
Emotion	9 (56%)	4 (100%)	4 (36%)	1 (100%)	5.657	.059
Cognition	13 (81%)	3 (75%)	2 (18%)	1 (100%)	0.336	.845
Self-care	7 (44%)	4 (100%)	3 (27%)	0%	7.135	.028
Pain	5 (31%)	2 (50%)	3 (27%)	0%	1.19	.552
Behavior	11 (69%)	3 (75%)	7 (64%)	1 (100%)	0.661	.719
General health	8 (50%)	4 (100%)	4 (36%)	0%	5.818	.055

ELCS, Extracorporeal life support; *ABAS,* The general adaptive composite score on the adaptive behavior assessment system 2nd edition; *DQ,* developmental quotient, which is the mental developmental index on the Bayley Scales of Infant Development II; *IQ,* intelligence quotient, which is the full scale IQ on Wechsler Preschool and Primary Scale of Intelligence III; *MAHSC,* the multiattribute health status classification system, parent completed. Motor or sensory disability was defined as cerebral palsy, visual impairment, or sensorineural hearing impairment (see Methods).The Psychomotor Developmental Index (PDI) from the Bayley Scales of Infant Development II was available for the 12 survivors assessed in the first 3 years of life, with a mean 66.2 ± 16.3; median 64, range 49 to 94.

(HR = 3.93; 95% CI 1.62–9.49; $P = .002$). For death by 10 days, the multiple logistic regression model consisted of variables significant at $P < .10$ on univariate analysis. In the adjusted model, lactate on admission to the PICU (OR 1.23; 95% CI 1.03–1.47; $P = .021$) and single ventricle anatomy (OR 24.98; 95% CI 2.01–310.14; $P = .012$) were associated with death by 10 days. To predict mental delay in the 16 survivors, we entered all dichotomous variables associated with delay at $P \leq .10$ (chromosomal abnormality) and all continuous variables significantly correlated with mental score at $P \leq .10$ (Table E2) into a forward multiple logistic regression. No variable was predictive of mental delay. Finally, all these variables for mental delay were entered into a stepwise multiple regression to predict the mental score as a continuous outcome. Three variables (time for lactate to fall to ≤ 2 mmol/L on ECLS, highest inotrope score during the first 120 hours of ECLS, and chromosomal abnormality) explained 76.7% of the variance in the mental score outcome (Table 5).

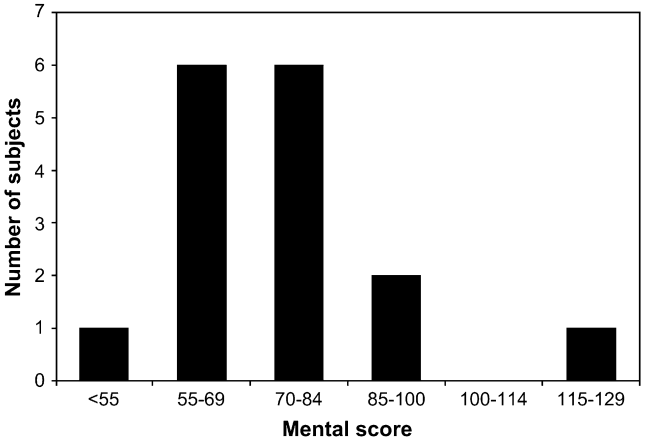

Figure 1. Distribution of mental scores in the 16 survivors of cardiac-related ECLS at less than 4.5 years of age. In a normal population, the mean score is 100 and SD is 15. Mental delay is considered a score 2 SD or more below the mean (≤70). The ECLS survivor scores are skewed to the left.

Discussion

Few reports describe the detailed survival and neurodevelopmental outcomes of patients receiving cardiac-related ECLS at age less than 5 years.[10] This study yields several important findings. First, 18 (46%) of 39 survived to hospital discharge, and the 2-year survival was 16 (41%) of 39. Second, neurodevelopmental concerns were identified in most survivors, with a mean mental score of 73 ± 16, mental delay in 8 (50%) of 16, motor or sensory disability in 2 (12.5%) of 16, and many having abnormal scores on the MAHSC. Third, a significant minority of survivors have ongoing concerns in general health (eg, growth, feeding, behavior, and pulmonary and cardiac medications). Fourth, on multivariable analysis, single ventricle anatomy and lactate on admission to the PICU were associated with death at 10 days and 2 years; and three variables (time for lactate to fall to ≤ 2 mmol/L on ECLS, highest inotrope score during the first 120 hours of ECLS, and chromosomal abnormality) explained 77% of the variance in mental score outcome. Finally, receiving

TABLE 4. Univariate (significant at $P < .10$) and multivariable Cox regression analysis for death by 2 years after ECLS

Variable	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Hospital weeks	0.10 (0.03–0.34)	.0002	0.09 (0.02–0.32)	.0002
Lactate on PICU admission	1.13 (1.05–1.21)	.0005	1.17 (1.08–1.27)	.0001
Platelets given over 120 h of ECLS ($mL \cdot kg^{-1} \cdot d^{-1}$)	1.03 (1.01–1.05)	.0035	—	—
PRBC given over 120 h of ECLS ($mL \cdot kg^{-1} \cdot d^{-1}$)	1.01 (1.00–1.01)	.0054	—	—
Single ventricle anatomy	2.50 (1.09–5.70)	.0297	3.93 (1.62–9.49)	.0024
Ventilator weeks	0.22 (0.05–0.88)	.0326	—	—
Pre-ECLS highest lactate	1.07 (1.00–1.14)	.0576	—	—
Admission weight (kg)	0.85 (0.71–1.03)	.0907	—	—
Seizures	1.52 (0.92–2.49)	.0995	—	—

ELCS, Extracorporeal life support; *PICU;* pediatric intensive care unit; *PRBC,* packed red blood cells; *HR,* hazard rate; *CI,* confidence intervals. Lactate on PICU admission in 16 survivors 5 (3) mmol/L, and in 23 nonsurvivors 11 (6) mmol/L ($P = .001$).

CPR before ECLS was not associated with death or a worse mental score outcome.

The rate of survival to discharge from the hospital (46%) is comparable with what has been reported in previous series of cardiac ECLS patients.[1,7-11] We also showed a small (5%) additional postdischarge mortality by 2 years after ECLS in this cohort of patients. Risk factors for an adverse outcome included single ventricle anatomy, chromosomal abnormality, younger age, and lower weight. All of these factors have been previously identified to be associated with increased mortality when using cardiac ECLS and likely represent the need for technically more complex surgical procedures and more difficult recovery from low cardiac output syndrome after CPB. Lactate concentrations are used clinically as an indicator of tissue hypoxia and have previously been shown to predict death and poor neurodevelopmental outcome in infants receiving respiratory ECLS and in infants after surgery for congenital heart disease.[19,20] On multivariate analysis, we found that lactate on admission to the PICU was predictive of death.

TABLE 5. Stepwise multiple regression to predict the mental score in 16 survivors of cardiac-related ECLS at < 4.5 years of age

Variable	Adjusted r^2	β	SE	*t*	Significance
Time for lactate to fall to ≤ 2 mmol/L on ECLS (h)	.484	.278	.067	4.145	.001
Highest inotrope score in first 120 h on ECLS	.687	.539	.191	2.821	.015
Chromosomal abnormality	.767	−12.31	5.289	−2.327	.038

SE, Standard error; *ECLS,* extracorporeal life support.

There are many potential causes of neurologic morbidity in pediatric patients who require ECLS for circulatory support. First, central nervous system abnormalities have been described in patients with congenital heart disease both before and after surgery.[12,21] Pre- ECLS events such as profound hypoxia and hypotension may occur before, during, or after surgery for congenital heart disease. The CPB techniques used (hypothermia, circulatory arrest, low-flow bypass, and anticoagulation with heparin) can contribute to postoperative neurologic morbidity.[22] ECLS-specific risks include ligation of the carotid artery and jugular vein, cerebral hemorrhage associated with altered cerebral autoregulation and prolonged systemic heparinization, microthrombi from the ECLS circuit, and any potential exposure to toxic agents.[23]

Our data indicate that over half (9/16 = 56%) of long-term survivors of cardiac ECLS have neurologic morbidity. It is encouraging that 7 of the 16 surviving patients were found to have no disability, but this is only 18% of the total patients who received cardiac ECLS. Chow and associates[9] reported that half of their long-term survivors of cardiac ECLS had adverse neurologic outcomes, determined by parental questionnaire rather than detailed neurodevelopmental testing; this resulted in only 17% of their patients who received cardiac ECLS ultimately surviving without neurologic morbidity. Hamrick and coworkers[10] reported cognitive outcomes of infants after cardiac ECLS. Of their 15 (28%) long-term survivors, 3 (21%) had a mental score between 1 SD and 2 SD below average, and 4 (29%) had a mental score more than 2 SD below average; this resulted in only 13% of their patients surviving neurologically intact. Given the high mortality rate reported in the literature for patients requiring cardiac ECLS as well as the many potential causes of central nervous system damage for these patients during their clinical course, the outcomes described above are not unexpected. We found that the potentially modifiable variables of time for

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lactate to fall to equal to or less than 2 mmol/L on ECLS and highest inotrope score during the first 120 hours of ECLS could explain 68.7% of the variability in mental outcome. This suggests that early attention to optimizing ECLS support may result in less neurologic morbidity in survivors.

Interestingly, the need for CPR before ECLS was not associated with an increased incidence of death or neurologic morbidity in our patients as it was in previous reviews of the Extracorporeal Life Support Organization registry as well as single-center series of cardiac ECLS patients.[9,10,24] This may be due to the more common availability and use of rapid response equipment and personnel in our center and in recent series.[25] As well, it has been shown that children with isolated heart disease have an improved survival after ECLS preceded by CPR when compared with those with other medical conditions.[26] This likely reflects a more reversible myocardial depression in patients with isolated heart disease than in those children with more complex medical conditions and multiple organ dysfunction syndrome. Similarly, we did not show an increased incidence of death in those patients who received renal replacement therapy during ECLS. Classically, the need for renal replacement therapy after surgery for congenital heart disease or during the provision of cardiac ECLS implied significant secondary organ dysfunction after periods of low cardiac output and was a risk factor for mortality.[27] Recently however, there has been emphasis placed on earlier implementation of renal replacement therapy in critically ill children.[28] We have adopted more liberal application of renal replacement therapy during ECLS, and this along with our relatively small number of patients likely accounts for a lack of association with death.

Our cohort included a significant number of patients with single ventricle anatomy (41%). Historically, patients with single ventricle anatomy have demonstrated lower rates of survival than other cardiac ECLS patients.[29] With the increased use of cardiac ECLS for patients with single ventricle anatomy over the past decade, their survivals have improved and may rival age- and size-matched patients with biventricular disease.[30] We found patients with single ventricle anatomy who were treated with ECLS to have a significantly higher 2-year mortality rate than patients with biventricular disease. Many of our patients with single ventricle anatomy had a Blalock–Taussig shunt; although we aimed for higher than usual ECLS flows to provide the systemic and pulmonary circulations in these patients, it is possible that the flows were not adequate and contributed to mortality. This is unlikely to account for the mortality difference inasmuch as the patients with single ventricle disease had similar lactates and inotrope scores compared with patients with biventricular disease.

Limitations of this report include the relatively small number of patients, which limits the power of any statistical analysis, and the retrospective collection of some of the acute care variables around the time of ECLS. Our patients did not have complete neurologic examinations or neuroimaging before being placed on ECLS; therefore, we could not examine whether preoperative neurologic abnormalities contributed to outcome. Strengths of this report include the inception cohort design with prospective complete and detailed neurologic testing of all survivors with no loss to follow-up, and the large amount of data available for analysis.

Although cardiac ECLS is a life-saving intervention, it is associated with a significant risk of mortality and neurologic morbidity. There is a need for vigilant surveillance of neurologic and psychosocial performance in survivors and provision of necessary rehabilitative treatments. Our data suggest that two potentially modifiable variables (time for lactate to fall to ≤ 2 mmol/L on ECLS and highest inotrope score during the first 120 hours of ECLS) account for 69% of the variance in mental outcome. Starting ECLS during ongoing CPR was not associated with mortality or mental outcome. It is hoped that future improvements in equipment, protocols, and the application of ECLS will translate into improved neurologic outcomes in future cohorts of patients.

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TABLE E1. Descriptive variables of 39 children with cardiac-related ECLS at < 4.5 years of age, by type of heart lesion

	Total (n = 39)	Single ventricle (n = 16)	Biventricle (n = 21)	Myocarditis (n = 2)	χ^2 or F	*P* value
Gender: male	20 (51%)	7 (44%)	12 (57%)	1 (50%)	.653	.721
Chromosomal abnormality*	4	3	1	0	2.171	.338
CPR before ECLS					2.681	.613
In OR	1 (3%)	1 (6%)	0 (0%)	0 (0%)		
In PICU	1 (3%)	3 (19%)	7 (33%)	1 (50%)		
Seizures					2.829	.587
Pre-ECLS	1	0	1	0		
During ECLS	6	2	3	1		
Re-CPB in OR	8 (21%)	4 (25%)	4 (19%)	0 (0%)	.741	.690
Sternum open pre-ECLS	29 (74%)	14 (88%)	16 (71%)	0 (0%)	7.344	.025
Indication for ECLS					3.886	.692
Fail weaning	13 (33%)	7 (44%)	6 (27%)	0 (0%)		
Hemodynamic	14 (36%)	4 (25%)	9 (43%)	1 (50%)		
Hypoxia	3 (8%)	2 (13%)	1 (5%)	0 (0%)		
CPR	9 (23%)	3 (19%)	5 (24%)	1 (50%)		
Cannulation site					10.482	.033
Chest	17 (44%)	6 (38%)	11 (52%)	0 (0%)		
Neck	20 (51%)	9 (56%)	10 (48%)	1 (50%)		
Multiple	2 (5%)	1 (6%)	0 (0%)	1 (50%)		
Left side vent	8/37 (22%)	4 (25%)	3 (16%)	1 (50%)	1.44	.487
Cardiac catheterization done	12 (31%)	5 (31%)	7 (33%)	0 (0%)	.955	.620
Residual lesion	11 (28%)	4 (25%)	7 (33%)	0 (0%)	1.140	.566
Sternal exploration first 5 d	22 (56%)	7 (44%)	14 (67%)	1 (50%)		.383
Hemofilter used	26 (67%)	10 (63%)	15 (71%)	1 (50%)	.589	.745
Time of surgery in relation to ECLS						
No surgery	1 (3%)	0 (0%)	0 (0%)	1 (50%)		
Before	31 (80%)	14 (88%)	17 (81%)	0 (0%)		
After	5 (13%)	2 (13%)	2 (10%)	1 (50%)		
During	2 (5%)	0 (0%)	2 (10%)	0 (0%)		
Age (d) ECLS started	206 (402)	203 (404)	215 (239)	120 (42)	.049	.952
Admission weight (kg)	5.2 (3.3)	5.2 (3.6)	5.1 (3.2)	5.4 (.7)	.010	.991
CPB time (min)	181 (122)	175 (86)	187 (145)	0	.082	.776
Aortic crossclamp time (min)	51 (41)	36 (28)	63 (45)	0	4.343	.045
DHCA time (min)	15 (19)	13 (18)	17 (20)	0	.507	.482
Inotrope score just before ECLS	34 (40)	28 (22)	40 (50)	15 (21)	.671	.517
12 h prior	10 (17)	11 (16)	11 (20)	0	.361	.700
24 h prior	7 (12)	9 (12)	7 (14)	0	.471	.629
Lactate just before ECLS	13 (6.9)	11.2 (6.3)	14.8 (7.6)	11.6 (.1)	.495	.615
Peak lactate on ECLS	11.1 (5.7)	9.6 (4.6)	12.5 (6.4)	8.7 (1.9)	1.431	.252
Time for lactate to fall to $\leq$ 2 mmol/L (h)	28.9 (27.9)	30.8 (34.6)	26.3 (22.7)	40.5 (31.8)	.286	.753
CPR duration before ECLS (min) (n = 12)	30 (21)	23 (16)	30 (21)	65	1.945	.199
Time for lactate to fall to $\leq$ 5 mmol/L (h)	8.2 (8.8)	5.5 (6.5)	10.5 (10.2)	6.5 (3.5)	1.540	.228
ECLS duration (h)	119 (81)	102 (59)	134 (96)	96 (39)	.761	.474
ECLS flow ($mL \cdot kg^{-1} \cdot min^{-1}$)						
At 12 h	108 (33)	120 (41)	100 (25)	101 (.7)	1.709	.195
24 h (n = 38)	111 (37)	125 (45)	103 (29)	95 (7)	1.784	.183
Inotrope score at 24 h on ECLS	10.3 (15.4)	6.8 (8.2)	13.6 (19.3)	5.0 (7)	1.017	.372
Highest inotrope score in 120 h on ECLS	18.5 (17.4)	12.0 (12.7)	24.8 (19.0)	5.0 (7)	3.485	.041
Fluid balance at 24 h on ECLS ($mL/kg^{-1}/day^{-1}$)	122 (126)	91 (133)	146 (124)	118 (66)	.864	.430
Cumulative fluid balance over duration of ECLS (mL/kg)	3.0 (4.1)	2.0 (4.3)	3.2 (4.2)	1.1 (.9)	.232	.794
PRBC at 24 h on ECLS (mL/kg)	171 (160)	201 (217)	147 (112)	196 (126)	.507	.607

TABLE E1. Continued

	Total (n = 39)	Single ventricle (n = 16)	Biventricle (n = 21)	Myocarditis (n = 2)	χ^2 or F	*P* value
PRBC average over 120 h on ECLS (mL/kg^{-1}/day^{-1})	118 (95)	123 (107)	118 (92)	78 (22)	.487	.619
Platelets at 24 h on ECLS (mL/kg)	40 (39)	54 (56)	30 (20)	40 (6)	1.783	.183
Platelets average over 120 h on ECLS (mL/kg^{-1}/day^{-1})	31 (23)	36 (32)	28 (17)	27 (11)	.438	.649
Plasma free Hb at 24 h on ECLS	321 (241)	307 (214)	320 (228)	450 (488)	.301	.742
Highest plasma free Hb in 120 h on ECLS	931 (933)	783 (629)	1019 (1142)	1214 (593)	.375	.690
Ventilator days	27 (29)	29 (38)	28 (20)	8 (6)	.459	.635
Hospital days	48 (46)	49 (67)	50 (25)	33 (6)	.114	.893
PELOD score just before ECLS	17 (7)	15 (5)	18 (9)	22 (1)	1.092	.346
PELOD score at 24 h on ECLS	17 (8)	17 (8)	17 (8)	24 (.7)	.687	.510
Highest daily PELOD score over 120 h on ECLS	20 (7)	20 (6)	20 (7)	28 (7)	1.377	.265

CPB, Cardiopulmonary bypass; *CPR,* cardiopulmonary resuscitation with chest compressions; *DHCA,* deep hypothermic circulatory arrest; *ECLS,* extracorporeal life support; *Hb,* hemoglobin; *OR,* operating room; *PELOD,* pediatric logistic organ dysfunction score; *PICU,* pediatric intensive care unit; *PRBC,* packed red blood cell transfusion. *Chromosomal abnormalities were deletion 22q11.2 (1 single ventricle, 1 biventricular), Turner syndrome (1 with single ventricle), and chromosome 22 duplication (1 with single ventricle).

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TABLE E2. Pearson product moment correlations of continuous variables with the mental score in 16 survivors on cardiac-related ECLS at age < 4.5 years

	Mental score	
	r	*P* value
Age ECLS started (d)	0.467	.068
Admission weight (kg)	0.505	.046
Time for lactate to fall to ≤ 2 mmol/L (h)	0.720	.002
Highest inotrope score in first 120 h on ECLS	0.662	.005
PRBC at 24 h on ECLS	0.008	.084

ELCS, Extracorporeal life support; *PRBC,* packed red blood cell transfusion.